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DLC

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/120,030	07/21/98	GOLDSTEIN	B	1102870-0456

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WHITE & CASE
PATENT DEPARTMENT
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036

EXAMINER	
BORIN, M	
ART UNIT	**PAPER NUMBER**
1654	4

DATE MAILED: 06/10/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/120,030	Applicant(s) Goldstein et al.
	Examiner M. Borin	Group Art Unit 1654

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-31 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-31 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Status of Claims

1. Claims 1-31 are pending.

Drawings

2. The drawings are objected because of the defects noted on the PTO-948.

Claim Rejections - 35 U.S.C. § 112, second paragraph.

3. Claim rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "glycopeptide" in claim 3 is vague and indefinite. It is not clear what glycopeptide out of myriads of known glycopeptides is encompassed by the claim. The term is not defined either in the art or in the specification.

Claim Rejections - 35 U.S.C. § 102 and 103.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 2, 4, 6, 9, 10,12-16, 19-21, 23-29 are rejected under 35 U.S.C. 102(b) as anticipated by Zygmunt (Fortschr. Armzneimittelforsch., 16, 309-333, 1972).

The instant claims are drawn to method of treating staphylococcal infection comprising administering effective amount of at least one lysostaphin analog and to the pharmaceutical composition comprising lysostaphin analog. A lysostaphin analog is defined as lysostaphin itself, recombinant lysostaphin, its mutants variants or any related enzyme that retains proteolytic activity.

Zygmunt

Zygmunt et al review properties of lysostaphin and its *in vitro* and *in vivo* applications. The reference teaches that lysostaphin is effective against wide variety of staphylococcal infection, and is more potent than penicillins. Lysostaphin is effective against strains of S. Aureus which are insensitive to other antimicrobial agents, such as cloxacillin, oxacillin, cephalothin (p. 314), and in particular, methicillin (p. 314,316,317). Similar to its *in vitro* effect, lysostaphin is effective *in vivo* against a wide variety of staphylococcal infections. The reference describes treatment of staphylococcal infections in various organs, such as kidney, heart valve (pages 319-325). The methods reviewed in Zygmunt anticipate the instantly claimed method of treating staphylococcal infections using lysostaphin.

In particular, in regard to claims 23-27, dosage of lysostaphin varies in the range of 0.5 to 50 mg/kg (p. 320, Table 4).

In particular, in regard to claims 19,20 the ways of administration are intravenous, intraperitoneal, topical, intranasal (pages 319-324).

In particular, in regard to claims 2, 21, combined therapy with other antimicrobials, such as methicillin, augments effect of lysostaphin (p. 322).

In particular, in regard to claims 28, 29, the reference teaches pharmaceutical compositions comprising lysostaphin, in particular suitable for parenteral administration.

6. Claims 1, 4, 9, 12-16, 28,29 are rejected under 35 U.S.C. 102(b) as anticipated by Stark (N.Engl. J. Med, 291, 239-240, 1974).

Stark (N.Engl. J. Med, 291, 239-240, 1974; see specification, p. 3, lines 21-25).

Stark et al describe that parenteral systemic administration of lysostaphin reduced bacteremia caused by strain of S. *Aureus* which proved to be resistant to methicillin, vancomycin and cephalothin. Single treatment with 500 mg of lysostaphin rapidly cleared microorganisms from pustule sites. The treatment removed staphylococci from blood, lungs,or abscess site

In particular, in regard to claims 28, 29, the reference teaches pharmaceutical compositions comprising lysostaphin, suitable for systemic or parenteral administration.

7. Claims 1, 4, 6, 7,10, 19, 20, 23-29 are rejected under 35 U.S.C. 102(b) as anticipated by Goldberg (Antimicrob. Ag. Chemother., 45-53, 1967).

Goldberg

Goldberg et al describe use of lysostaphin in treatment of staphylococcal endocarditis in dogs. Lysostaphin was administered intravenously in doses 5-50 mg/kg at intervals 1 to 24 h. Lysostaphin treatment resulted in decreased number of staphylococci in lung, liver, spleen, kidney, aortic and mitral valves. See abstract.

In particular, in regard to claims 28, 29, the reference teaches pharmaceutical compositions comprising lysostaphin, in particular suitable for parenteral administration.

8. Claims 1, 17, 18, 28, 31 are rejected under 35 U.S.C. 103(a) as obvious over Zygmunt or Stark or Goldberg as applied in the rejections above and further in view of Oldham.

The instant claims are drawn to the use of recombinant lysostaphin.

The primary references, applied as discussed above, do not teach the use of recombinant lysostaphin.

Oldham (J. Dairy Sci., 74, 4175-4182, 1991)

Oldham et al teach that recombinant lysostaphin is effective against *S. Aureus* at low concentration of 5 µg/ml. See abstract.

It would have been obvious to one skilled in the art at the time the invention was made to be motivated to use recombinant lysostaphin instead of the natural lysostaphin used in the primary references, because it is easier to produce a recombinant analog of a natural product and because Oldham demonstrated that recombinant lysostaphin has high antimicrobial activity similar to the natural product.

9. Claims 1, 4-6, 28, 29 are rejected under 35 U.S.C. 103(a) as obvious over Zygmunt or Stark or Goldberg, and further in view of admitted prior art.

The instant claims are drawn, in part, to the use of lysostaphin analogs. It is well known in the pharmaceutical art to develop and use new, improved analogs of known pharmaceuticals. As mechanism of action of lysostaphin is the lysis of the membrane wall

of staphylococci, it would be obvious to develop and use new, more potent analogs of this well known antibiotic. See, for example lysostaphin analogs described in specification, p. 1, lines 26-34.

10. Claims 2,3,21,22, 28-30 are rejected under 35 U.S.C. 103(a) as obvious over Zygmunt and further in view of Dixon.

Zygmunt reference is applied as above. The instant claims are drawn to combination therapy of lysostaphin and another antimicrobial, in particular rifamycin or a glycopeptide. Zygmunt does not teach combined use of lysostaphin and rifamycin or a glycopeptide. However, Zygmunt teaches that a single dose of lysostaphin is effective against staphylococcal infection only for limited time, and it is preferable to follow lysostaphin with another antibiotic. Further, Dixon et al. teach that it is preferable to use lysostaphin in combination with other antimicrobials because a single dose usage of lysostaphin reduces dangers of hypersensitivity reaction. See p. 63, first paragraph. Because combination therapies for treatment of staphylococcal infection are well-known in the art and because it would have been desirable to use plural therapies in order to maximize the probability that staphylococcal infection is minimized, it would be *prima facie* obvious to one of ordinary skills in the art at the time the invention was made to be motivated to use the lysostaphin not only as a sole active pharmaceutical agent, but also in combination with other commonly used antimicrobials, such as rifamycin or glycopeptides.

11. Claims 4, 7,8, 10, 11 are rejected under 35 U.S.C. 103(a) as obvious over Zygmunt or Stark. The references are applied as discussed above. The references do not teach all possible sites of infections as recited in the claims. However, as Zygmunt teaches that lysostaphin is effective against more than 300 staphylococcus species and suggests its wide use at various locations, and as Stark suggests use of lysostaphin for treatment of human staphylococcal infections in lung, liver, brain, endocardium, and bone, it would have been obvious to an artisan to apply this versatile antimicrobial at the sites which require antimicrobial treatment with the expectation, in the absence of evidence to the contrary, that such treatment will be successful.

Prior art made of record

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Harrison (Can. J. Microbiol., 13, 93-97, 1967)

Harrison et al teach treatment of three staphylococcal infections with lysostaphin: acute peritonitis, leg edema, and dermal ear infection. Lysostaphin is administered in dose of less then 0.0007 mg/kg intraperitoneally or 0.5 mg/kg subcutaneously.

Pulverer (Z. Med. Microbiol., 154, 40-48, 1968)

Pulverer teaches that lysostaphin is an effective antimicrobial against 355 Staphylococcal strains of human origin, including methicillin-resistant strains. See abstract.

Zygmunt (Applied Microbiology, 16, 1174-1178, 1968)

Zygmunt et al. teach that lysostaphin is bactericidal against sixteen methicillin-resistant strains of *S.aureus*. See abstract. Growth of all 16 strains was inhibited by lysostaphin concentrations of 0.78 µg/ml or less. See p. 1175, second paragraph.

Conclusion.

13. No claims are allowed

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Cecilia Tsang can be reached on (703) 308-0254. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June 2, 1999

mlb

MICHAEL BORIN, PH.D
PATENT EXAMINER